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INTRODUCTION

Continuous separation of mixtures of immiscible liquids featuring different wettability properties can be achieved using microporous membranes. However, in order to achieve common industrial acceptance, this technology must demonstrate factual scalability and robustness in operation under realistic (and thus challenging) operating scenarios. It is the purpose of this paper to demonstrate the applicability of a mini-scale hydrophobic membrane based separator for the continuous hydrolysis and liquid-liquid (L-L) separation of an organic and aqueous mixture, while critically evaluating the practical operability and limitations of micro/mini-scale-based L-L separators in the context of continuous pharmaceutical manufacturing (CPM).

PROCESS DESCRIPTION

The synthesis of *cis*-zuclopenthixol – a product of H. Lundbeck A/S – is studied. The manufacturing process consists of the process steps described in Figure 1. The paper will focus on the continuous hydrolysis of the alkoxide product obtained from a continuous Grignard alkylation reaction and especially on the subsequent continuous separation of the organic and aqueous phases.

Figure 1: Schematic description of the production process (CTX - 2-Chlorthioxanthen-9-one; GR - Grignard reagent; THF - Tetrahydrofuran; Allylcarbinol - 9-Allyl-2-Chlorothioxanthen-9-Ol 9H-thio xanthen-9-ol; Butadiene -

Continuous hydrolysis of the alkoxide product

The alkoxide (unhydrolized allylcarbinol) dissolved in THF reacts with water containing a small amount of HCl. This reaction is performed in a 1/8 inch PTFE tube reactor using a T-connection from which segmented flow is generated. The reaction is exothermic and the heat is released using a water bath. The alkoxide is hydrolized while producing Mg salts which are solubilised by HCl forming $MgCl_2$. The amount of water is regulated so that the Mg salt concentration is below saturation, thereby decreasing the risk of blockage due to precipitation of these salts.

Continuous L-L separation

The hydrolysis reaction forms an organic phase and an aqueous phase which are immiscible thanks to the salting-out effect caused by the Mg salts. Otherwise the two solvents (THF and water) would be totally miscible. In our case study the phases have similar densities, and therefore separation by decantation would require prohibitively long settling times, while having a non-perfect phase separation. Therefore a PTFE membrane mini-separator based on capillarity and surface tension differences [1] was developed and tested. A plate coalescer has also been built, and the performance obtained with the two separation devices in terms of operability and flexibility has been compared [1]. The PTFE membrane mini-separator provided a perfect separation of the organic and aqueous mixtures at all concentrations tested, for different flow rates and flow ratios of the alkoxide solution and the acidic water solution. The concentration of the active pharmaceutical ingredient was measured by HPLC in both the organic and aqueous phases, while the amount of water in the organic phase and the concentration of THF in the aqueous phase were measured using at-line near-infrared (NIR) spectroscopy measurements. The results indicate that not only a perfect separation of the API is obtained in the organic phase, but also a slight decrease in the amount of water in the organic phase is obtained thanks to the hydrophobic membrane.

CONCLUSIONS

Micro-scale technology can be extremely helpful when establishing a continuous pharmaceutical production process, but it must be optimally combined with mini/meso-scale reactors/separators when required. A mini-scale PTFE membrane separator was built enabling the continuous hydrolysis and separation of an organic solution containing an API, and an aqueous solution containing Mg salts. Some of the flow rates used and the conditions of the experiment are very much alike the ones required for industrial scale production. Therefore only a small effort is expected to scale-up/out this process, which is by far one of the major advantages of this technology.

REFERENCES

[1] Cervera-Padrell, A.E., Morthensen, S.T., Lewandowski, D.J., Skovby, T., Kiil, S., Gernaey, K.V., Continuous hydrolysis and L-L phase separation of an active pharmaceutical ingredient using a mini-scale PTFE membrane separator (in preparation).